Remarks

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Support for Amendments

Support for the foregoing amendment to claim 1 may be found throughout the specification. Specifically, support for the amendments may be found, *inter alia*, at pages 4-5 and 9-10, and in Example 1 at pages 28-30. Support for new claims 54-56 may be found throughout the specification, for example, at page 4, lines 20-22 and page 9, lines 20-21. Accordingly, the present amendment does not add new matter, and its entry is respectfully requested.

II. Status of the Claims

Upon entry of the foregoing amendment, claims 1, 2, 6, 12, 16-20, 22, 25, 28-32, and 54-56 are pending in the application, with claim 1 being the sole independent claim.

III. Summary of the Office Action

In the Office Action dated October 3, 2001, the Examiner has made two rejections of the claims. Applicants respectfully offer the following remarks to overcome these rejections.

IV. The Rejection Under 35 U.S.C. § 102(e) Is Traversed

In the Office Action at pages 2-3, section 2, the Examiner has rejected claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31, and 32 under 35 U.S.C. § 102(e) alleging that the claims are anticipated by Burmer, U.S. Patent No. 5,726,022 (hereinafter "Burmer"). Applicants respectfully submit that this rejection is not applicable to claim 1 as currently amended.

In making this rejection, the Examiner first characterizes the disclosure of Burmer by contending that:

> Burmer discloses that an adaptor with a restriction site is ligated to a first nucleic acid sample and optionally the adaptor may contain a ligand binding end. Further, Burmer discloses that if the first and the second nucleic acid fragment [sic] are amplified, they are amplified with primers containing a ligand binding end and a sequence complementary to the adaptors (See column 2, lines 39-48). The teachings are inherent that the primer of Burmer contains all the limitations as recited in claims 1, 2, 12, 16-17, 25, 28, 29.

Office Action at page 2, section 2.

A reference anticipates a claim "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) The adapters of Brumer are DNA oligonucleotides and are ligated to restriction digested cDNA molecules. Brumer characterizes the unique aspect of his invention as "the use of a restriction enzyme to isolate the target duplex DNA molecule from a hybridization mixture." (Column 1, lines 57-60) Since Brumer does not teach the use of an RNA template, Applicants respectfully submit that Brumer does not anticipate claim 1 (and hence all the claims that depend from claim 1), and respectfully request reconsideration and withdrawal of this rejection.

V. The Rejection Under 35 U.S.C. § 103(a) Is Traversed

In the Office Action at pages 3-5, sections 3 and 4, the Examiner has rejected claims 1, 2, 6, 12, 16, 17-19, 25, 28-29, and 31 under 35 U.S.C. § 103(a), alleging that the claimed invention is obvious over the teachings of Frohman (PCR protocols, 1990, pg 28-38, hereinafter Frohman) in view of Lohman, *et al.* U.S. Patent No. 5,631,147 (hereinafter Lohman). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner characterizes the disclosure of Frohman as teaching an adapter primer containing restriction sites. (Office Action page 4). After acknowledging that Frohman does not teach that the adapter primers comprise the ligands required by claim 1, the Examiner attempts to remedy the deficiencies of Frohman by combining the teachings of Frohman with those of Lohman. The Examiner goes on to assert:

> One of ordinary skill in the art would have been motivated to combine the teachings of Frohman and Lohman et al. to make instant invention with a reasonable expectation of success because in order to label the adapter primer of Frohman, the method of Lohman et al. involves using the primer attached to ligand and such that the movement of the amplification of the method of Frohman is tracked. Thus it would have been prima facie obvious to carry out the method as claimed.

Office Action pages 4 and 5, section 4.

Applicants respectfully submit that the Examiner has failed to make out a *prima facie* case for the obviousness of the claimed invention as the Examiner has not provided any motivation to combine the teachings of the two references to reach the claimed invention. The Examiner seems to be asserting that the inclusion of the ligand as taught by Lohman would be used to track "the movement of the amplification of the method of Frohman." Applicants do not understand what is meant by tracking the movement of an amplification

reaction nor why one would wish to do it. There is no suggestion in the cited art that the "movement" of an amplification reaction is or should be tracked. Since the references themselves do not provide motivation to combine and the Examiner has failed to provide any other source of motivation to combine, a *prima facie* case of the obviousness of the claimed method has not been made out.

In addition to failing to identify motivation to combine the references, the present rejection is improper because the references themselves can not be combined. MPEP 2143.01 reads in pertinent part:

> If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion to make the proposed modification.

The purpose of the Frohman reference is the cloning of full length cDNA molecules. In order to clone the amplified fragments, the restriction-site-containing primers of Frohman are digested with restriction endonucleases to permit directional cloning of the amplified fragments. (see page 32) Thus, in order to carry out the intended purpose of the methods of Frohman, the product of the amplification reaction must be a nucleic acid molecule that *can be cleaved* in both strands to produce the customary "sticky ends" for subsequent ligation.

In contrast to the cloning methods of Frohman, the purpose of the methods disclosed in the Lohman reference is the *in situ* amplification of target nucleic acid sequences (column 3, line 58). In order to accomplish this, the reaction requires that a nick be introduced in the amplified product. The nicking activity "is of great importance, as it is nicking which perpetuates the reaction and allows subsequent rounds of target amplification to initiate." (Column 7, lines 54-56) This nick is introduced by cleaving only one strand of the amplified product using a thermostable endonuclease. The amplification product is prepared

by incorporating modified nucleotides into either the primer or the amplification reaction to produce one strand of the amplified product that is resistant to cleavage. (Column 7, lines 59 et seq.) Thus, in order to carry out the intended purpose of the methods disclosed in the Lohman patent, the product of the amplification reaction must be a nucleic acid molecule that *cannot be cleaved* but instead can be partially cut to produce the required single strand nick.

Clearly, the methods of the two references require completely different products be prepared in the amplification reactions. Further, the products are mutually exclusive; the cleavable product of the Frohman method will not work in the Lohman method and non-cleavable product of the Lohman reaction will not work in the Frohman method. Thus, any combination of the methods of the cited references would result in the methods being rendered unfit for their intended purposes. In view of this, Applicants respectfully submit that there is no motivation to combine the cited references and request reconsideration and withdrawal of this rejection

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Robert W. Esmond

Robert W. Esmond
Attorney for Applicants
Registration No. 32,893

Date: Jan. 31, 2002

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

Version with markings to show changes made

1. (Twice Amended) A method for making a nucleic acid molecule comprising:

(a) mixing [a] one or more nucleic acid templates with (i) one or more polypeptides having polymerase activity and/or reverse transcriptase activity and (ii) a primer-adapter nucleic acid molecule, to form a mixture; and

(b) incubating said mixture under conditions sufficient to make a first nucleic acid molecule complementary to all or a portion of said template and comprising said primer-adapter nucleic acid molecule,

wherein said primer-adapter nucleic acid molecule comprises one or more ligands and one or more cleavage sites and one or more of said templates is an RNA molecule.